Biochemical Actions of Hormones

VOLUME VII

Edited by

GERALD LITWACK

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Preface

This collection extends the pattern of previous volumes in this treatise. The intent is to cover a broad range of subjects representing research efforts at the cutting edge of hormone action. Sometimes there are noticeable gaps in the coverage by previous volumes and specific contributions are sought to fill these.

There are a variety of subjects included in this volume. A. White reviews recent developments on hormones of the thymus. J. A. Gustafsson and collaborators review new evidence on the regulation of liver steroid and drug metabolism by the hypothalamus and anterior pituitary. S. M. McCann and co-authors provide up-to-date information on the regulation by neurotransmitters in the hypothalamus of LHRH and somatostatin. F. J. Ballard presents a review of hormonal regulation of protein degradation in liver and in isolated cells which complements a contribution in a previous volume by H. E. Morgan and collaborators on the regulation of protein synthesis and degradation in heart and skeletal muscle. J. N. Fain presents a timely article on the hormonal regulation of lipid mobilization from adipose tissue. Steroid hormone mechanisms are represented in three contributions: U. Gehring reports on cell genetics of glucocorticoid responsiveness and L. K. Miller and S. J. Higgins review the mero-receptor and androgenic regulation in male accessory tissues, respectively. Finally, J. Baxter's group brings us up to date on current views of the molecular biology of thyroid hormone action.

It is hoped that this approach to timely critical reviews by experts in their respective fields will serve the advancement of the expanding subject of hormone action.

As this volume was near completion, Dr. Abraham White died suddenly on February 14, 1980. I decided that a fitting tribute would be the dedication of this volume to his memory. Dr. White's secretary, Edna Van der Vort, and Mrs. White generously made available the photograph which is reproduced in the early pages. I called on Dr. Maynard Makman, a long-time associate and friend of Dr. White, to prepare a brief tribute, which appears in the front matter.

GERALD LITWACK

Abraham White (1908–1980)

Abraham White (1908–1980)

The contributions of Abraham White to biochemistry, endocrinology, and medicine span a period of over 50 years. Abraham White was a scientist, educator, and author, as well as a founder and organizer of a school of medicine; in each of these capacities his accomplishments were distinguished and many. His career was rich and fulfilling and his energies undiminished to the end. He was widely recognized as an authority in biochemistry and as a leading medical educator. His numerous awards included the Eli Lilly prize, the Borden Award, and election to the National Academy of Sciences.

Abe White was born in Cleveland. He received a bachelor's degree from the University of Denver in 1927 and a Ph.D. from the University of Michigan in 1931. At the University of Michigan he studied with the great American biochemist Howard B. Lewis. The first publication of which Abe White was senior author concerned the metabolism of sulfur-containing amino acids and was published in 1932 in the *Journal of Biological Chemistry*. His early work concerned primarily the chemistry and metabolism of amino acids, but as early as the 1930s his interests broadened to include insulin and the pituitary hormones. From 1931 until 1948, Dr. White was at the Yale University School of Medicine, and in 1948 he left to become Professor and Chairman of the Department of Physiological Chemistry at the University of California School of Medicine in Los Angeles. During the 1940s his research interests focused on the mechanism of action of adrenal corticosteroids. During the next several decades he made many important contributions to our understanding of the action of steriod hormones and the influence of steroids on

lymphoid tissue. Abe White was one of the first investigators to recognize the importance of the thymus gland with respect to both immunological and endocrine functions. Some of these investigations were summarized in a review he co-authored with Allan Goldstein that appeared in the first volume of "Biochemical Actions of Hormones."

In the late 1940s, Abe White, together with Drs. Philip Handler, DeWitt Stetton, and Emil L. Smith, first became interested in writing a textbook of biochemistry. In 1954 "The Principles of Biochemistry," with Abraham White as first author, was published by McGraw-Hill. This book, now in its sixth edition, is one of the most widely recognized and used texts of biochemistry. Dr. White was intensely involved in the creation and further evolution of this work. His careful, thoughtful, and deep commitment to this endeavor clearly exemplifies his breadth and devotion as scientist and educator.

Abe White was the first faculty member of the Albert Einstein College of Medicine and the first chairman of the College's Department of Biochemistry. He was instrumental in the creation of the Medical School as well as in its further growth to become a leading medical institution. From 1952 to 1972 he was an Associate Dean and Professor and Chairman of Biochemistry at the Albert Einstein College of Medicine. After 1972, although he became a Professor Emeritus at Einstein, he and his wife, Edna, moved to Palo Alto where he continued to pursue an active research program at Syntex Laboratories, as well as to teach at Stanford University School of Medicine.

The field of hormone research has benefited immensely from the research efforts of Dr. White. Those efforts span most of his professional career. Included are important contributions to hormone biochemistry, physiology, and pharmacology. Of particular significance is his early work on insulin, the crystallization of prolactin and studies of its properties, and studies of other pituitary hormones including the biochemistry and actions of adrenocorticotropin. Probably of even greater importance is his later work concerning the glucocorticoids and his studies of thymosin. He was involved actively and energetically in research concerning the purification and action of thymosin up to the time of his death. His latest studies and ideas concerning thymic hormones form the first chapter of this volume.

My association with Dr. White began 16 years ago when I became a member of his Department. Bernyce Dvorkin and I worked closely with him in studies of the influence of steroid hormones on lymphoid cells until he left Einstein. We all found this an exciting and challenging endeavor. In this as in other contexts Abe White had an amazing ability to communicate and share his wide range of knowledge as well as his enthusiasm for new ideas and findings. It seemed that there was nothing in the current literature of which he was not aware, and he had a unique

perspective on past accomplishments. He was always interested in the ideas of others. He did not avoid controversy but carefully considered points of view considerably different from his own. Abe was a teacher, collaborator, and friend to me. The ambience of his department provided a marvelous atmosphere for work and for development of both students and faculty. He was always optimistic and could see the positive side of any situation or problem. Most important of all, he communicated a sense of the excitement and purposefulness of scientific work that left a lasting impression on all those with whom he came into contact. His legacy extends far beyond his work, as considerable as that is, to many individuals whose lives were permanently enriched by him.

MAYNARD H. MAKMAN
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CHAPTER 1

Chemistry and Biological Actions of Products with Thymic Hormone-Like Activity

Abraham White

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I. INTRODUCTION

Nine years have elapsed since the initial volume of this treatise presented a review of the thymus as an endocrine gland, its hormones, and their actions (Goldstein and White, 1971). In the intervening period, significant progress has been made in the further delineation of the endocrine role of the thymus and in the isolation and characterization of some of its hormonal products. These achievements have provided the basis for initial clinical trials with certain of the thymic hormones. The preliminary results encourage a continuing, comprehensive examination of the potential therapeutic value of these hormones, and other preparations, in a broad variety of diseases whose etiology may have an impaired, immunological component.

The rapidity with which interest in the thymus and thymic hormones has expanded during the 1970s is reflected by the publication of two volumes (Luckey, 1973; Van Bekkum, 1975), several symposia (Friedman, 1975), and a number of reviews (Trainin, 1974; White and Goldstein, 1975; Bach and Carnaud, 1976; Bach, 1977; Bach *et al.*, 1978; A. L. Goldstein *et al.*, 1978, Goldstein, 1978; Low and Goldstein, 1978; Trivers and Goldstein, 1979) on the subject of the thymus and its hormones.

The growth of interest in the thymus and thymic hormones not only has resulted in a very large number of publications, but also has provided evidence that a variety of fractions and preparations from thymic tissue and blood, as well as other tissues, may synthesize and secrete both polar and nonpolar compounds that may be eligible for designation as thymic hormones. These newer data have been obtained during a period of more precise dissection of specific cell populations, whose immunological responses may be modulated by the secretions of the endocrine thymus. Hence, in this volume it appears desirable to attempt to review and evaluate present knowledge of the thymus as an endocrine gland, its hormones, and thymic hormone-like factors.

This chapter discusses the more highly purified and characterized thymic hormone-like products that have been isolated from thymic tissue or from blood. Relatively specific criteria have been selected for deciding which preparations to include. The most critical assessment for acceptance of any putative endocrine product as a hormone is its ability to replace specific functions of the extirpated or absent gland in experimental conditions that would, in the lack of activity of the product, fail to ameliorate the deleterious consequences of loss of the organ. For the thymus, past experience indicates that a product with thymic hormone or thymic hormone-like activity should exhibit activity in one or more of the following biological models:

1. Amelioration of immunological impairment in
   a. The neonatally thymectomized animal

b. The adult thymectomized, immunosuppressed animal
c. The nude, athymic mouse

2. Other biological criteria
Enhancement of immunological response evaluated in a variety of *in vitro* and *in vivo* assays reflecting the roles of the two major classes of lymphoid cells basic in host immunity, namely, the T and B cells. In addition, a third cell, the macrophage, has been utilized in assays designed to test production of macrophage inhibitory factor (MIF).

This author will focus on the thymus, its hormones, and on other soluble products with thymic hormone-like activity relevant to the functions of the thymus in the classical sense as an endocrine gland influencing selected immunological parameters. However, the functions of the thymus of a nonendocrine nature will not be presented. These functions include the thymus as a vital site for the direction, development, and selection of immunological properties inherent in mature thymocytes, e.g., cells involved in self- and non-self-recognition, and the role of the thymus as reflected in certain cell–cell interactions.

Although this chapter contains numerous references to the thymus as an endocrine gland, this last designation is based primarily on historical reasons and earlier concepts of endocrinology. We are presently in the midst of a revolution in thought concerning basic definitions and relationships in endocrinology. The term *hormone* was defined by Bayliss and Starling (1904) "as a substance produced in one part of the body and carried by the blood or lymph to some other part, the activity of which is thereby modified." However, the concepts of an *endocrine gland* and a system of glands in a discipline of endocrinology, are being drastically modified. Thus, the presence of identical hormonal peptides in the brain and the gastrointestinal tract, neither structure being characteristically an "endocrine gland," suggests, rather, the distribution of dispersed cells in the mammalian organism which have a common embryonic origin, and may therefore synthesize and secrete identical chemical substances with properties of a hormone.

It may be noted that this presentation does not include other types of immune-enhancing products that have been described as altering host immunological competence but are, on the basis of present evidence, unrelated to the role of the thymus in the broad area of immunobiology. These products include, for example, levamisole (Symoens and Rosenthal, 1977) and the peptidoglycans (Chedid and Audibert, 1977) that have significant activity as assessed in selected assays reflecting immunological responsivity. These compounds, however, as well as products isolated from other organs [e.g., the bursa of the chicken (Brand *et al.*, 1976) and the bovine parotid gland (Mizutani *et al.*, 1977a, 1978)], although enhancing certain immunological parameters, such as lymphocyte numbers and antibody production when tested in appropriate